Table 13: Biosimilars

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SCOPE:

In May of 2019, FDA issued new draft guidances on development of biosimilars regarding the design and evaluation of comparative analytical studies for biosimilarity as well as interchangeability. While a number of biosimilars have been approved in the US (26 as of November 2019), none are designated as Interchangeable (as of December 2019). What are the implications for approval and interchangeability of new biosimilars?

QUESTIONS FOR DISCUSSION:

1. How does this new guidance compare to historical development of biosimilars?
2. Has the FDA Guidance impacted your development programs? Your approach to establishing analytical comparability?
3. How has the guidance impacted regulatory evaluation of biosimilar applications?
4. Can sponsors share their thoughts on the new guidance?
5. Are the product differences between different territories impactful for evaluation of biosmilarity?

DISCUSSION NOTES:

The membership of the table included industry and regulators.

In one member question, it was acknowledged that the statistical approach for comparative analytical assessment is different in the new draft guidance (more like the EMA). The question was posed, if you are currently using the previous approach and have agreements with the FDA, do you keep the older approach or do you switch? The consensus opinion was that BLA has to be submitted according to the current guidance. Some members indicated they were continuing with the current guidance, while others are changing to align with the draft guidance.

The question was asked, how many would follow the new draft guidance for new BLA? It was noted that half group was actively developing biosimilars. One opinion was that it would be program dependent, with Regulators wanting to talk and see what makes sense for each situation. It was asked, How far back would you go to implement new guidance? Most felt that it would be more work to go back to re-analyze and most would to some point in development, but not to the beginning of a program.

It was discussed that the guidance is not a checklist list but a new way of looking at biosimilarity. It was suggested that Phase III clinical lots, which are close to the BLA, should be done closer to the draft guidance.

There was a member question on the frequency of guidance changes. The consensus was that it does happen, but not that often. It was noted that previously the goal was to look for identical molecules, and, and that was nearly impossible. Now, differences are expected, but the question is; are they significant? (Fingerprint like similarity seems to be out of favor/has ambiguous meaning.)

It was noted that if a characteristic does not match the reference product, it may be acceptable, provided it's shown that the difference is not meaningful. This would require additional testing, and additional assays to asses these differences would need to be added to release specifications.

The question was asked, since biosimilars are evolving, how have they been received by FDA? Opinions shared included that unmet medical needs is the mission so agencies don't favor biosimilars, while a contrary opinion is that price does address a need! The opinion that guidance draft or final is non-binding was given. It was noted that questions could be brought to the agency with in a Type I meeting for example.

A member asked a question on guidance in general; is the expectation that the guidance will be followed when the filing is reviewed? It was thought that guidance is an attempt to show current thinking on general level, and to guide, and leave open where there is flexibility. However, the answer would depend on what aspect of the guidance you're asking about. (For example, product quality could be different.) It was noted that biosimilars are also eligible for Type I meetings.

The topic of Interchangeability was introduced, and it was noted that we don't yet have anything that qualifies. It was acknowledged that approval requires extra work from clinical side, and CMC is also impacted. It was thought that with time there could be a shift in the originator product and that presents a possible issue for establishing interchangeability. As an example, a process change could yield a shift which is still within specification. The question was then, what does originator do? And what is the patient experience? It was thought that once approved, it is your own product, however it was noted this is not the case in the US. (Post approval in US, the dosage/formulation/route of administration cannot be changed. For example, subcutaneous administration of an IV formulation biosimilar is NOT a biosimilar in the US.) Discussion continued, asking if a reference product was approved with a new route of administration, then what would it be? It was noted that there are cases of multiple routes of administration for the same drug. It was thought that to address these questions it was necessary to talk to the agency to see what the package would look like for a new or different route of administration, and it would not be a simple analytical comparison.

The question was raised, what makes more sense, to compare post-approval batches to the innovator or to your trend? It was thought that this would be handled similar to an innovator change. (For example, using the data collected since approval; look at totality of the data, and that it is necessary to understand the quality of the product.) It was noted that even though many biosimilars are approved, post approval is a new area for the agency as well. It was suggested that the same principles used for lifecycle management should be applied here as well, and that the industry and regulatory thinking is evolving. It was suggested that there may be other ways of looking at the data without just re-doing the whole analytical assessment. Discussion of Interchangeability continued and it was noted that Interchangeability not just analytical data and that biosimilarity and interchangeability are different.

The opinion was shared that the US Agency has been more science based and flexible than other agencies, and more consistent. It was suggested that the ability to meet on regular basis was helpful to guide decision making processes, and that other agencies may not be as open to meetings.

The question was raised if there was a harmonized way to do drug development for biosimilars, as it is necessary to get samples from US, JPN, EU, etc.? The thought was that agencies wouldn't know for sure if manufacturing is different for different sources. But to get approval in the US the biosimilar must be compared to originator in the US; the agencies must operate within the statute. It was noted that guidance tries to provide a pathway, and the agency tries to keep a standard approach (e.g. 3 way analytical, 3 way PK bridging is the path for now).

The question was raised, since in the guidance the 3 way bridge must connect to clinical experience, what can you do if the some of the lots are no longer be available? Can you substitute something that's analytically comparable? It was discussed that the comparative analytical assessment must include clinical lots in PK study/clinical study, however not every lot is tested for every attribute and not every clinical lot needs to be included. However, for bridging the expectation is 3 way analytics. This was considered to be an excellent question, with no clear cut answer, only that the approach needed to be scientifically sound.

The question of what to do if the originator stops making the drug in the US was raised. It was noted that this has happened in small molecule world, not biologics yet and that there is no clear guidance on this issue.

In further discussion, it was noted that the elimination of equivalence was welcomed as some statistical approaches could yield false positive/negatives. It was also noted that much of the roundtable conversation illustrates how guidance is thought to be cast in stone, but we should be looking to have a conversation the agency, and scientifically justify the approach a program is taking. Guidance expresses current thinking, and questions come when developers are not within that approach. It was also noted that 'justify another approach' is just that. (Intent is to provide clarity, not to make a cookie cutter approach.)

Another question was raised; what are agency expectations for QBD as it the approach is different from company to company? Opinions offered were that QTPP should be expected with a BLA. (It's the defining the space that we want to go into with the product profile.) It was questioned if this was really needed, and it was thought that if a different approach was taken, it would need to be justified.